NeuroImage: Clinical 23 (2019) 101906

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Axonal degeneration in Parkinson's disease – Basal ganglia circuitry and D2 receptor availability

Esther Annegret Pelzer[a,*], Corina Melzer[a], Anna Schönberger[b], Martin Hess[a], Lars Timmermann[b,c], Carsten Eggers[b,c], Marc Tittgemeyer[a,d]

[a] Max-Planck-Institute for Metabolism Research Cologne, Germany, Gleueler Str. 50, 50931 Cologne, Germany
[b] Department of Neurology, University Hospital Cologne, Kerpener Str. 62, 50937 Cologne, Germany
[c] Department of Neurology, University Hospital Marburg, Baldingerstr., 35039 Marburg, Germany
[d] Cologne Cluster of Excellence in Cellular Stress and Aging-Associated Disease (CECAD), Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany

ARTICLE INFO

Keywords:
Parkinson's disease
BG circuitry
D2 receptor polymorphism
Motor output
Treatment response

ABSTRACT

Basal ganglia (BG) circuitry plays a crucial role in the control of movement. Degeneration of its pathways and imbalance of dopaminergic signalling goes along with movement disorders such as Parkinson's disease. In this study, we explore the interaction of degeneration in two BG pathways (the nigro-striatal and dentato-pallidal pathway) with D2 receptor signalling to elucidate an association to motor impairment and medication response.

Included in the study were 24 parkinsonian patients [male, 62 years (± 9.3 SD)] compared to 24 healthy controls [male, 63 years (± 10.2 SD)]; each participant passed through three phases of the study (i) acquisition of metadata/clinical testing, (ii) genotyping and (iii) anatomical/diffusion MRI.

We report a decline in nigro-striatal ($p < .003$) and dentato-pallidal ($p < .0001$) connectivity in the patients compared to controls, which is associated with increasing motor impairment (relating to nigro-striatal, $r = -0.48$; $p < .001$ and dentato-pallidal connectivity, $r = -0.36$; $p = .035$). Given, that variations of the *ANKK1* Taq1 (rs 1,800,497) allele alters dopamine D2-dependent responses, all participants were genotyped respectively. By grouping patients (and controls) according to their *ANKK1* genotype, we demonstrate a link between D2 receptor signalling and decline in connectivity in both investigated pathways for the A1- variant (nigro-striatal pathway: $r = -0.53$; $p = .012$, dentato-pallidal pathway: $r = -0.62$; $p = .0012$). In patients with the A1+ variant, we only found increased brain connectivity in the dentato-pallidal pathway ($r = 0.71$; $p = .001$) correlating with increasing motor impairment, suggesting a potentially compensatory function of the cerebellum.

Related to medication response carriers of the A1+ variant had a better drug effect associated with stronger brain connectivity in the nigro-striatal pathway ($r = 0.54$; $p < .02$); the A1- group had a good medication response although nigro-striatal connectivity was diminished ($r = -0.38$; $p < .05$); these results underscore differences in receptor availability between both groups in the nigro-striatal pathway. No effect onto medication response was found in the dentato-pallidal pathway ($p > .05$).

Interplay between basal ganglia connectivity and D2 receptor availability influence the clinical presentation and medication response of parkinsonian patients. Furthermore, while current models of basal-ganglia function emphasize that balanced activity in the direct and indirect pathways is required for normal movement, our data highlight a role of the cerebellum in compensating for physiological imbalances in this respect.

1. Introduction

A cell loss in the substantia nigra (compact part; SNpc) due to axonal degeneration has been proposed to be causative for the pathological striatal output (Tagliaferro and Burke, 2016). Studies estimated that 40–60% of nigral cells are lost and synaptic function is reduced by up to 80% before signs enable a clinical diagnosis of Parkinson's disease (Fearnley and Lees, 1991). On the way to understand the pathophysiological cascade of Parkinson's disease and to find new neuro-protective therapies, it becomes more and more obvious, that axonal degeneration even occurs before nigral cell bodies die (Tagliaferro and Burke, 2016; Burke and O'Malley, 2012; O'Malley, 2010). Dopaminergic

* Corresponding author at: Translational Neurocircuitry Group, Max-Planck-Institute for Metabolism Research, Gleueler Str. 50, 50931 Cologne, Germany.
E-mail address: esther.pelzer@sf.mpg.de (E.A. Pelzer).

https://doi.org/10.1016/j.nicl.2019.101906
Received 12 February 2019; Received in revised form 3 June 2019
Available online 21 June 2019

projection axons from the midbrain to the striatum are crucial for locomotion and reward learning with sub-second precision, a function that is crucially affected in Parkinson's disease (Howe and Dombeck, 2016). An increased vulnerability of dopaminergic axons due to the genetical risk has been discussed to predispose the disease onset (Burke and O'Malley, 2012). But also an accumulation of misfolded proteins, mitochondrial dysfunction or reactive oxygenic stress yielding to axonal transport impairment, was hypothesized to be involved in the development of Parkinson's disease (Trimmer et al., 2009; Dauer and Przedborski, 2003). Here, alpha-synuclein, a presynaptic neuronal protein that is genetically and neuro-pathologically linked to Parkinson's disease, seems to play a specific role in the pathogenesis and the increased vulnerability of dopaminergic axons; the accumulation of this protein has been proposed to specifically alter axonal transport by disturbing e.g. intracellular transport pathways to lysosomes (Abeliovich and Gitler, 2016). These findings are in line with results of new antibodies and staining protocols, where alpha-synuclein pathology is abundant in axons and the degeneration begins in the distal axon and proceeds retrograde yielding to an affection of cell bodies (Tagliaferro and Burke, 2016). An additional suggestion facilitating the aetiology of parkinsonian symptoms is the special arborisation of nigral neurons and loss of dopaminergic terminals (Matsuda et al., 2009). Especially the long, thin unmyelinated and poorly myelinated axons have been proposed to be the most vulnerable (Braak and Del Tredici, 2004): Dopaminergic neurons of the SNpc are of this type (Tagliaferro and Burke, 2016). By influencing the striatal plasticity of medium spiny neurons in the striatum axonal degeneration in the nigro-striatal pathway contributes pathophysiological to the development of Parkinson's disease.

Phylogenetically, the BG circuitry is an ancient brain structure, comprising of a direct pathway and indirect pathway controlling behaviour like locomotion, reward learning and eye-movement (Grillner and Robertson, 2016). According to the classical view on BG organisation (DeLong, 1990) the striatum is the main input structure of the BG, containing 95% GABA-ergic spiny striatal projection neurons: (1) the first expresses dopamine D1 receptors, is excited by dopamine, and projects directly to the output neurons of the basal ganglia [substantia nigra, reticular part (SNr) and internal globus pallidus (GPi)]. These neurons represent the 'direct pathway' through the basal ganglia. Activation of these neurons is thought to facilitate movement (Kravitz et al., 2010). The second type expresses dopamine D2 receptors, is inhibited by dopamine and is called 'the indirect pathway'. In this pathway projections are sent via inhibitory, external part of the external globus pallidus (GPe) and the excitatory subthalamic nucleus (STN), which in turn targets the output level of the basal ganglia (GPi and SNr). In contrast to the first pathway, activation of indirect-pathway neurons is thought to reduce movement (Kravitz et al., 2010). A balance between the D1 and D2 system is necessary for sufficient motor control (Cox et al., 2015) and avoidance-based decisions (Frank and Hutchison, 2009); a dysbalance between these two systems might be causative in the development in parkinsonian symptoms (Shen et al., 2008) influencing the glutamatergic output of the thalamus (Lanciego et al., 2012). It is worth mentioning, that next to striatum, recent studies also discuss the STN as an input structure of the BG circuitry via hyperdirect pathway (Deffains et al., 2016).

In the striatum medium spiny neurons are heterogeneous in their expression of dopamine receptors and their plasticity (Gerfen et al., 1990). Whereas D1 dopamine receptor signalling promotes long-term potentiation (Reynolds et al., 2001; Calabresi et al., 2007), D2 dopamine receptor signalling promotes long-term depression (Kreitzer and Malenka, 2007). In animal models of Parkinson's disease, where striatal dopamine levels are low, both forms of synaptic plasticity in medium spiny neurons appear to be lost, which suggests that dopamine receptor signalling is necessary for their induction (Calabresi et al., 2007; Kreitzer and Malenka, 2007). Current models of the basal ganglia function herewith emphasize, that balanced activity of medium spiny neurons of both (the D1 and D2) pathways, is required for normal movement, and that movement disorders result from imbalanced pathway activities (Obeso et al., 2008). Recently, Parker et al. (2018) expanded the classical view and found that normal movement involves activation of clusters of the D1 and D2 system; in the parkinsonian state they found, that D1 activation is reduced and D2 activation is increased. Clusters of activated D1 striatal projection neurons are smaller than in the normal state, and active D2 striatal projection neurons are less clustered, opening a more complex view on the D1 and D2 interplay.

Additional to the D1 and D2 system further satellite systems have been posited to explain clinical manifestations in Parkinson's disease like tremor and non-motor symptoms (Obeso et al., 2010): (i) a striato-nigro-striatal loop (Haber et al., 2000), (ii) a 'hyperdirect' projection system as well as additional projections to the STN (Forstmann et al., 2012) and (ii) multisynaptic connections from the cerebellum, exerting influence on the indirect projection system (Bostan et al., 2010; Hoshi et al., 2005). Next to the above proposed nigro-striatal system, also the dentato-pallidal projection influences the motor output in Parkinson's disease (Wu and Hallett, 2013).

The A1 allele of the D2 (*ANKK1*) TaqIA (rs1800497) SNP regulates dopaminergic D2 receptor availability (Pohjalainen et al., 1998; Eisenstein et al., 2016), primarily in the striatum. The TaqIA SNP is associated with a mutation producing a single amino acid change within the substrate-binding domain of the ankyrin repeat and kinase domain containing 1 (*ANKK1*) protein (Neville et al., 2004) and is in linkage disequilibrium with the D2 receptor locus (Zhang et al., 2007). Healthy individuals who carry the A1 allele (A1+; risk allele), compared with those who do not (A1-; wild type), have shown diminished striatal D2 receptor density (Jönsson et al., 1999) and reduced glucose metabolism in regions involved in reward processing and receiving dopaminergic innervations (Noble et al., 1997). Results of the latter studies have, however, to be interpreted carefully due to small sample sizes, methodological differences, variable effect sizes and because the Taq1A is not located in the D2 gene itself (Eisenstein et al., 2016; Smith et al., 2017; Gluskin and Mickey, 2016). Although the role of the D2 polymorphism as a risk factor for Parkinson's disease has been discussed controversially (Tan et al., 2003), meta-analyses of the polymorphism have shown an increased risk of the development of Parkinson's disease by 13% in Europeans (Dai et al., 2014; McGuire et al., 2011).

In this study we strive to scrutinize (i) connectivity within BG circuitry in vivo at the example of the nigro-striatal and dentato-pallidal pathway. As diffusion MRI and diffusion tractography has been repetitively shown to be successful in the assessment of macroscopic brain connectivity in vivo (Jbabdi et al., 2015), we use this method to assess putative neurodegenerative decline with disease state in Parkinson patients: (ii) connectivity changes in relation to clinical markers of disease severity; (iii) the D2 receptor availability in association with the clinical presentation of the individual patients and their medication response.

2. Material and methods

All tests were performed after informed consent in conformance with the declaration of Helsinki and in accordance to the local ethics committee (http://www.medfak.uni-koeln.de). The project was divided into three subparts: (i) acquisition of behavioural data, the (ii) determination of gene variants and (iii) the MRI acquisition.

2.1. Behavioural data

We included 24, predominantly akinetic-rigid, male PD patients and 24 healthy volunteers matched for age, gender, and handedness as controls in the experiment. The patients were diagnosed with PD according to the Movement Disorder Society diagnostic criteria (Postuma et al., 2015) and therefore subjects without any clinical response to levodopa treatment were excluded from the study. Also patients with

relevant concomitant neurological diseases were pre-selectively excluded from the study like patients with signs and symptoms of dementia, or past history of stroke or brain surgery. There was also no history of toxin exposure, head injury, encephalitis, and metabolic diseases. Due to the fact that gender makes a difference, especially in the analysis of brain connectivity relayed on diffusion MRI, we only included male participants in the study (Gong et al., 2011). The 24 healthy controls were acquired in analogous fashion. The behavioural part comprised a video acquisition of the UPDRS, part III. Hence two independent movement disorder specialists rated the UPDRS motor scale (part III) in (a) un-blinded and (b) blinded condition in order to reduce bias by the observers; here the %-responsiveness to standardized soluble L-Dopa (200 mg) was calculated additionally to the degree of motor impairment (reflected by the UPDRS motor scale, part III in the OFF state). Individual rating factors of the observers subjectively influence the UPDRS outcome; an independent and blind rating together with an unblinded rating enhances the reliability of the scoring. We additionally determined the medication response for both gene polymorphisms:

$$Med\,\mathrm{Re}\,sp = \frac{UPDRS\,(OFF) - UPDRS\,(ON)}{DD}$$

MedResp = Medication Response.

UPDRS = Unified Parkinson's disease Rating Scale (OFF: after medication withdrawl; ON: with dopaminergic medication).

DD = Disease Duration.

Additionally, the disease duration and levodopa equivalent dosage (LEDD) was acquired (Tomlinson et al., 2010). In all patients and controls handedness was tested by the laterality index (LI; (Oldfield, 1971)) and a dementia was excluded. For further information of the behavioural testing see Supplementary Material 1.

2.2. Genotyping

After the acquisition of clinical items a blood sample was taken. Isolation of DNA form was performed using the QIAamp DNA Blood Mini Kit (# 51106, QIAGEN) according to the manufacturer's instructions. Concentration and quality of the DNA were determined with an ND-1000 UV/Vis- Spectrophotometer (Peqlab). SNP genotyping for rs1800497 (*ANKK1*) was performed with 20 ng of DNA in triplicates using allelic discrimination assays (TaqMan SNP Genotyping Assays, Applied Biosystems by Invitrogen). The genotyping PCR was performed on a 7900HT Fast Real-Time PCR System (Applied Biosystems), and the resulting fluorescence data were analysed with Sequence Detection Software version 2.3 (Applied Biosystems). Subgroups were defined according to the gene variant defined by the *ANKK1* TaqIA (rs1800497) SNP [A1- (wild type): GG; A1 + (risk allele): AG, AA].

2.3. MRI acquisition

Diffusion and structural MR images were acquired of all patients and controls in the 3 T Tim Trio Siemens Scanner, Erlangen. The structural data sets were acquired in a 12-channel array head coil and a maximum gradient strength 40 mT/m with a whole-brain field of view (T1-weighted: MDEFT3D; TR = 1930 ms, TI = 650 ms, TE = 5.8 ms, 128 sagittal slices, resolution = 1 × 1 × 1.25 mm^3, flip angle = 18°, image dimension 256 × 256 × 128; T2-weighted: RARE; TR = 3200 ms, TE = 482 ms, resolution = 1 × 1 x 1 mm^3, image dimension 240 × 256 × 176). Furthermore diffusion-weighted data sets were acquired using spin echo planar imaging (SE-EPI; TR = 9000 ms, TE = 87 ms, resolution 1.7 × 1.7 × 1.7 mm^3, flip angle: 90°, image dimension: 220 × 220 × 123 mm^3, direction of slice acquisition: transversal, data matrix: 128 × 128 × 72, number of acquisitions: 1, b-values: 1000 s/mm^2 (60), 0 s/mm^2 (6), no cardiac gating) with double-spin echo preparation (Reese et al., 2003); next to the 72 slice protocol in some patients we had to increase the number of slices to 90 to ensure all relevant parts of the cerebellum were included due to different head size and the mobility of the neck of the participants; next to the TR = 11,200 ms, however, all diffusion parameters remained unchanged. For both measurements diffusion weighting was isotropically distributed along 60 diffusion-weighted directions (b-value = 1000 s/mm^2). Additionally, in each subject six data sets with no diffusion weighting were acquired and interleaved after each block of 6 diffusion-weighted images as anatomical reference for motion correction. The dMRI data were acquired after the T1- and T2-weighted images in the same scanner reference system.

2.4. Processing of MRI data

All processing steps were performed with the FMRIB Software Library (FSL, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) in version 5.0.4. These processing steps involve: (1) preprocessing of MR images, (2) generation of anatomical masks per investigated area, and (3) post-processing including diffusion tractography to quantify brain connectivity. All preprocessing scripts are available under https://github.sf.mpg.de/TNC/kfo-parkinson.git and detailed by pipeline visualisations provided in the Suppl. Figs. 1 and 2.

The segmentation protocol applied for all areas considered in this study has been recently published in a prior study, for further details see Pelzer et al. (2013). We here briefly summarize: After nonlinear registration of T1- and T2-weighted images into standard space, two anatomical experts who were blinded with regard to the patient criteria and any clinical information performed mask outlining. Masks were traced in MNI-152-1 mm space using fslview (http://fsl.fmrib.ox.ac.uk/fsl/fslview/) in order to get one “template” mask per sub-region. Mask locations were chosen by comparison of different anatomical atlases (Morel, 2007; Mai et al., 1997; Naidich et al., 2009; Schmahmann et al., 1999; Schaltenbrand and Wahren, 1977). Manually outlined seed and target masks were then transformed from standard space into diffusion space. The two anatomical experts again visually checked all transformed masks for correctness after transformation.

Manually outlined seed- and targetmasks were transformed from standard space into diffusion space utilizing applywarp by the application of the postmat-function (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT/UserGuide#Now_what.3F_–_applywarp.21). Consecutively, FAST was applied on every B0-image, which segments a 3D image of the brain into different tissue types [cerebrospinal fluid (CSF), grey matter (GM), white matter (WM)]. Focus of our interest was the segmentation of CSF, where registration deficits close to the ventricle were automatically corrected by a subtraction of the CSF segment. The two anatomical experts again visually checked all transformed masks for correctness after transformation.

The mask generation of the substantia nigra required a separate procedure in order to reach conclusive evidence in the segmentation of such a small and heterogeneous brain region (Theisen et al., 2017): In an initial step we delineated the substantia nigra (SN) by two neuroanatomical experts (E.A.P., Andreas Hintzen) on T2-weighted images in standard space. Here, the protocol was chosen according to the MRI-atlas of Naidich et al. (2009): Nigral borders were defined on T2-weighted images (Atasoy et al., 2004); masks were initially labelled in axial plane and then controlled in coronal and sagittal plane. Included in the mask were both, the compact part and the reticular part of SN due to limitations in image resolution; please note, that the ventral tegmental area (VTA) and the medial lemniscus cannot safely be excluded in labelling process either. As bordering criteria the following structures were considered: anteriorly the cerebral peduncles, ventromedially the red nucleus, and latero-dorsally the STN. Thus, deliberately, SN masks were labelled slightly “bigger” in order to comprise the complete structure. To reduce variability and enhance specificity regarding the part of the nigra that is connected with the putamen (mainly fibres from and to the compact part), diffusion tractography was now applied. Thus, in a second step and according to a protocol

outlined in Menke et al. (2010), we traced all voxels within this SN delineation to the putamen. Collectively, the segmentation-based approach for SN only included voxel, which were connected with the putamen, what enabled a comparison of the degree of connectedness between the patients.

Before the application of the tractography algorithm, the sizes of all masks [caudate nucleus; dentate nucleus, globus pallidus, putamen, substantia nigra and thalamus] were tested for significant differences between patients and controls in an unpaired sample *t*-test and in an F-test to compare variances. Mask sizes of the generated masks were analysed in diffusion space (for further details see Suppl. Table 2). There were no significant differences in the mask sizes between subjects and patients tested in an unpaired sample t-test ($p > .05$) and no significant differences in an F-test analysis to compare variances ($p > .05$). For further information of the mask development, see Suppl. Fig. 4.

The FDT-toolbox of FSL (version 5.0.4) was applied for tractography (Behrens et al., 2007). We calculated probability distributions between seeds- and target regions by the application of FSL's probabilistic tractorgraphy algorithm (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#PROBTRACKX_probabilistic_tracking_with_crossing_fibres): Number of samples was $P = 5000$, the number of steps $S = 2000$ with a step length of 0.5 and a curvature threshold of $c = 0.2$. All target regions were defined as waypoint masks. The following connections were analysed: (1) nigro-striatal (2) striato-nigral (3) dentato- thalamo-striato- pallidal and (4) pallido-striato-thalamo-dentatal connections. The way PROBTRACKX works is that it generates sample "streamlines", or trajectories, to build up a distribution on the location of a connection; this correlates with the anatomical distribution of fibres. Here, we were interested in the probability of the tract starting at A and passing through B. In other words, this is equal to the number of streamlines from A that reaches B (call this K), divided by the total number of streamlines from A (call this N). In order to get K, we run PROBTRACKX with A as a seed and B as waypoint; then K was stored in a text file called waytotal. In order to get N, we multiplied the number of voxels in A by the number of samples per voxel (default = 5000):

$$\phi(A + B) = \frac{K}{N}$$

with ϕ = connection probability starting in A passing through B, K = waytotal, and N = number of voxels in A * 5000 (default).

Connectivity values for the nigro-striatal and the dentato-pallidal pathway were determined by the arithmetic mean of "forward" and "backward" tractography. The anatomical delineation of the nigro-putaminal pathway (see Suppl. Fig. 5) was verified by comparison to Carpenter and Peter (1972), who defined -in non-human primates- this tract by starting in the SNpc then passing through the pallidum and to projecting in the putamen [see Fig. 3B in (Carpenter and Peter, 1972)]; furthermore, cerebello-thalamo-basal ganglia interconnectivity (Pelzer et al., 2017; Hintzen et al., 2017) and the anatomical reliability of tracking the dentato-pallidal pathway (see Suppl. Fig. 6) has been demonstrated recently in a separate feasibility study [see Pelzer et al., 2013].The resulting connectivity values for each individual patient were referenced to the mean brain connectivity of the healthy control group to include the variance.

2.5. Statistical analysis

Connectivity information of 48 hemispheres for each group was included into statistical analyses. All statistical analyses were then performed with PRISM (http://www.graphpad.com/scientific-software/prism/). Connectivity values were normally distributed in the nigro-striatal pathway ($p > .05$) whereas dentato-pallidal connection were not ($p < .0001$) according to a D'Agostino & Pearson omnibus normality test. Due to this deviation from the normal distribution we performed a logarithmic transformation of the dentato-pallidal brain connectivity values before the analysis of correlation and linear regression. We had no missing data in the group. To address the question of the in vivo measurability of neurodegeneration, we first compared (i) brain connectivity between patients and controls; secondly (ii) we performed correlation analyses with the clinical markers and (iii) implemented resulting dopaminergic gene variants of the TaqIA (rs1800497) SNP located in the *ANKK1* gene in the analysis. Alpha-error correction was performed with the Holm-Sidak method at a significance level of 0.05 for multiple comparisons (UPDRS-III, LEDD, DD, AR and TD Score). We subdivided the patient's group into two subgroups (A1-: GG; A1+: AG, AA), where the A1- subgroup consisted of 14 patients and A1+ group of 10 patients; we then performed a subgroup analysis of the individual *ANKK1* gene variant (A1+, A1-) correlating brain connectivity of the subgroup with the motor impairment and the medication response.

3. Results

We were able to anatomically depict the nigro-putaminal (Suppl. Fig. 5) and dentat-pallidal pathway (Suppl. Fig. 6). Our analysis revealed a significant reduction of connectivity in the nigro-striatal ($p < .003$; Fig. 1a) as well as in the dentato-pallidal pathway ($p < .0001$; Fig. 1c) in 24 patients compared to 24 healthy controls.

Moreover, we investigated whether a link exists between this decline in connectivity and clinical scales, e.g. the occurrence of motor impairment. To that end, we analysed the association between connectivity measures, the UPDRS -part III-, akinesia and tremor sub-scores after dopaminergic withdrawal: (a) a decline in nigro-striatal connectivity was associated with the UPDRS-III ($r = -0.39$; $p < .01$), the akinesia score ($r = -0.48$; $p < .001$; Fig. 1b) as well as with disease duration ($r = -0.31$; $p < .03$) and the levodopa equivalent dosis (LEDD, $r = -0.34$; $p < .029$). This means that lower connectivity values in the nigro-striatal pathway yielded to higher clinical impairment in the individual patient; (b) a decline in dentato-pallidal connectivity also correlated with the akinesia score ($r = -0.36$; $p < .035$; Fig. 1d, left), but not with any other marker of clinical impairment or the LEDD. However, a non-linear decline in connectivity in this pathway indicates a different, much more accelerated underlying degeneration pattern as compared to the nigro-striatal pathway (Fig. 1d, right).

To consider the question whether alterations in D2 receptor signalling predicts disease state or dopaminergic treatment response, we tested for an interaction between the respective measures and gene variations in *ANKK1*. No significant differences between allele-carriers and the wild type were found for any clinical parameter: disease duration, UPDRS-III, akinesia-rigidity, tremor score, or LEDD.

Yet, patients with the A1- variant (i.e., higher striatal D2 receptor availability) exhibited an association between nigro-striatal connectivity and motor impairment (AR-score: $r = -0.53$; $p = .012$; UPDRS-III: $r = -0.46$; $p = .030$; see Fig. 2); this was also found for the A1- variant in the dentato-pallidal connectivity regarding motor impairment (AR-score: $r = -0.62$; $p = .0012$). Individuals, with the at-risk A1+ allele (i.e., lower striatal D2 receptor availability) showed no significant alteration in connectivity and motor impairment for both, nigro-striatal and dentato-pallidal connectivity. Remarkably, this effect was reversed relating higher brain connectivity of the dentato-pallidal connectivity (AR: $r = 0.71$; $p = .001$; UPDRS-III: $r = 0.51$; $p = .043$; Fig. 3) to higher motor impairment.

Furthermore, in A1+ individual's nigro-striatal connectivity was associated with medication response ($r = 0.54$; $p < .02$; Fig. 4): patients holding the at-risk A1+ variant had only a good medication response when connectivity in the nigro-striatal pathway was high. For A1- individuals, however, connectivity and medication were negatively correlated, i.e. the therapeutic effect was high, when brain connectivity was low ($r = -0.38$; $p < .05$).

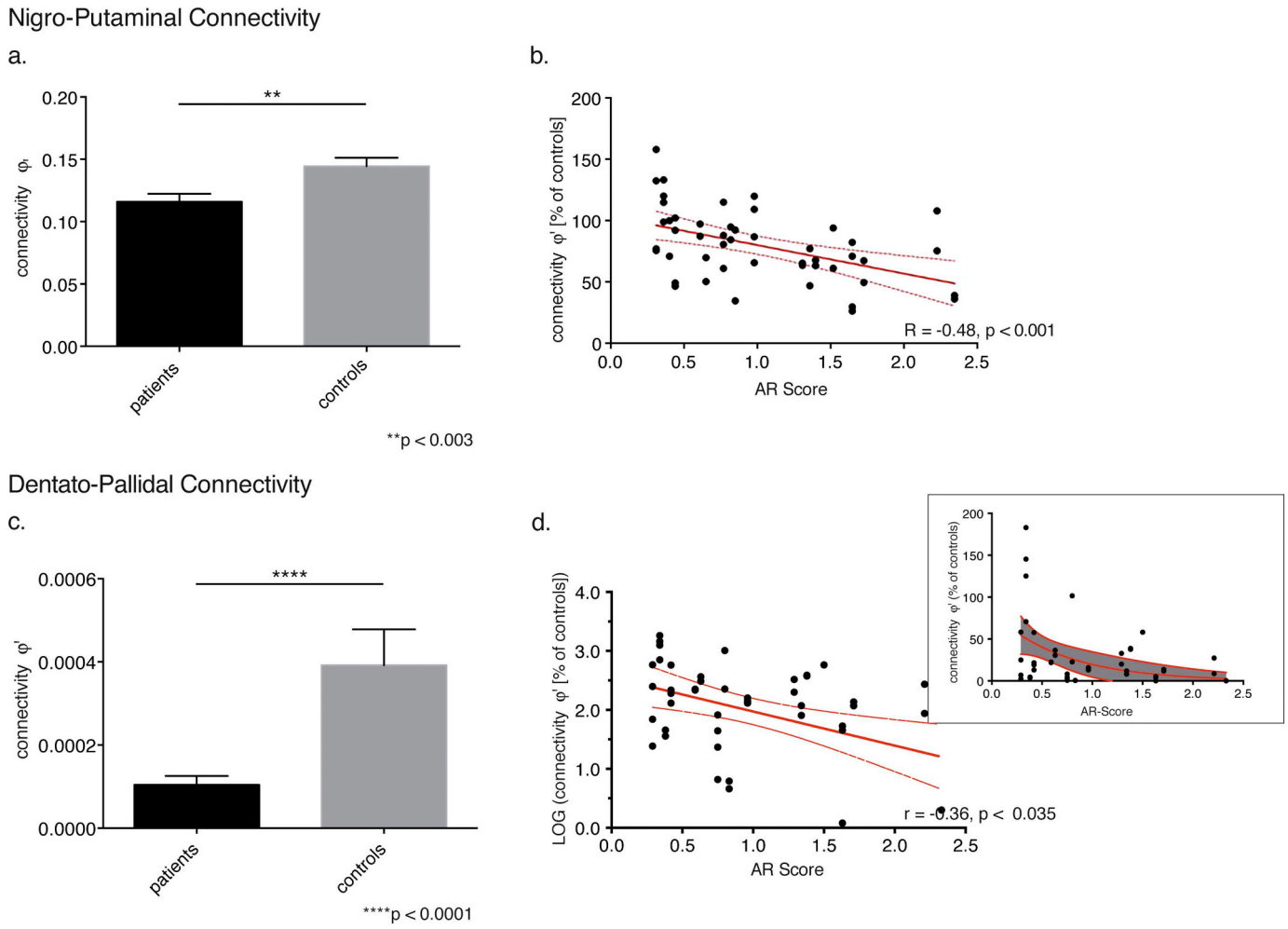

Fig. 1. Overview of nigro-striatal and dentato-pallidal connectivity analyses.
(a) Connectivity within the nigro-striatal pathway in a comparison between patients and controls [$p < .003$]; (b) correlation of connectivity in the nigro-striatal pathway with the mean akinesia-rigidity (AR) score [$r = -0.48$; $p < .001$]; (c) connectivity in the dentato-pallidal projections between patients and controls [$p < .0001$]; (d) correlation of connectivity in dentato-pallidal projections with the mean AR score [$r = -0.35$; $p < .035$].

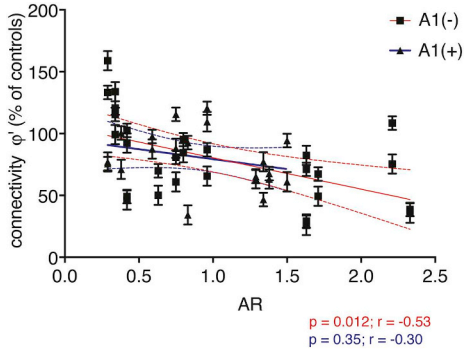

Fig. 2. Degeneration pattern of individual *ANKK1* gene variants in the nigro-striatal system.
In dependency of the individual gene variants [risk allele (A1+); wild type (A1-)] we found different degeneration strengths in the nigro-striatal system; patients with A1- variant had a significant negative correlation with brain connectivity and the motor impairment ($r = -0.53$; $p = .012$), whereas patients with the risk allele remained non-significant ($r = -0.30$; $p = .35$).

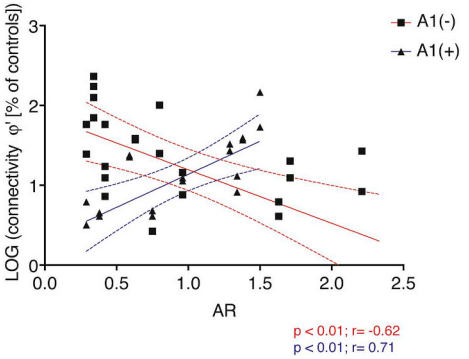

Fig. 3. Degeneration pattern of individual *ANKK1* gene variants in the dentato-pallidal system.
In dependency of the individual gene variants [risk allele (A1+); wild type (A1-)] we found antagonistic degeneration patterns in the dentato-pallidal system. Whereas patients with the A1- variant had decreasing connectivity in the dentato-pallidal pathway ($r = -0.62$; $p < .01$), patients with the A1+ variant had an increase of brain connectivity ($r = 0.71$; $p < .01$), which might be explained by a (potentially) compensatory role of the cerebellum.

4. Discussion

Collectively, with this study we present three important findings: (1) nigro-putaminal and dentato-pallidal connections both decline in the course of Parkinson's disease, i.e. this decline is associated with impaired motor function – notably, the decline in dentato-pallidal connections seem to be accelerated in comparison to the putative

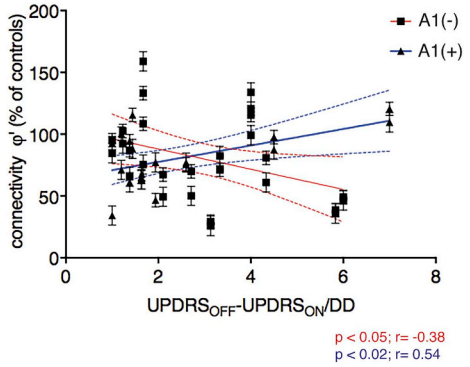

Fig. 4. Influence of *ANKK1* gene variants on the medication response.
Differences in D2 receptor availability as predicted by the gene variant [risk allele (A1 +); wild type (A1-)] interact with response to medication and nigro-striatal connectivity. Due to the reduced receptor density, patients with the risk allele (A1 +) had only a good medication response, when brain connectivity in the nigro-striatal system was high ($r = 0.54$; $p < .05$); this was reversely found for the A1- group ($r = -0.38$; $p < .05$), where due to the high D2 receptor density a good medication response was even found when brain connectivity was low.

degeneration of the nigro-putaminal pathway; (2) by grouping patients (and controls) according to their *ANKK1* genotype, we demonstrate a link between D2 receptor signalling and decline in connectivity in both investigated pathways for the A1- variant (i.e. wildtype). In patients with the A1 + variant, we found increased brain connectivity in the dentato-pallidal pathway ($r = 0.71$; $p = .001$) correlating with increasing motor impairment, suggesting a potentially compensatory function of the cerebellum; (3) finally, differences in D2 receptor availability as predicted by gene variant interact with response to medication and nigro-striatal connectivity, but not cerebellar connectivity.

4.1. The nigro-striatal pathway

Degeneration of nigro-striatal projections has been described to be highly present in patients with Parkinson's disease (Kordower et al., 2013). Interestingly, our results from this in vivo study echo the effect of decreased connectivity in nigro-striatal connections in parkinsonian patients during increasing disease duration and motor impairment, as shown by neuro-pathological analyses (Paulus and Jellinger, 1991). We found a linear decrease of nigro-striatal pathway connectivity with increasing akinesia score, as hypothesized in the BG model by Lanciego et al. (2012). As mentioned above, an additional suggestion facilitating the aetiology of parkinsonian symptoms is the special arborisation of nigral neurons and loss of dopaminergic terminals (Matsuda et al., 2009). Especially the long, thin unmyelinated and poorly myelinated axons have been proposed to be the most vulnerable (Braak and Del Tredici, 2004). It has been suggested that D2 receptor signalling plays a specific role in modulating the extent of the terminal arbour of SNpc neurons (Parish et al., 2001). Our findings underscore the role of the D2 receptor in the development of Parkinson's disease, with different neurodegenerative patterns for carriers of different variants of the *ANKK1* gene. Moreover, dopamine D2 receptors regulate the bridging collateral density from nigro-striatal neurons to the pallidum associated with increased pallidal inhibition. Bridging collateral density modulates herewith the functional balance of basal ganglia circuitry. These findings mirror the complex interplay between influence of gene variants of the D2 receptor and brain plasticity (Cazorla et al., 2014). Our study is to our knowledge the first, which combines structural connectivity with a gene polymorphism implicating in D2 receptor signalling in Parkinson's disease, and it demonstrates a different degeneration pattern for carriers of different allele variants for nigro-striatal connectivity.

4.2. The dentato-pallidal system

The existence of cerebellar projections to the pallidum has been repetitively proven in the macaque monkey (Hoshi et al., 2005), in cats (Ichinohe et al., 2000) and in healthy humans (Pelzer et al., 2013). In our study dentato-pallidal connectivity revealed a non-linear decline in connectivity following disease severity in PD, which is distinctly different from the decline in the nigro-striatal pathway. An implication of the cerebellum in the dopaminergic system (Giompres and Delis, 2005) and a structural involvement of the cerebellum in the development of parkinsonian symptoms is well established (Kakita et al., 1994). Its impact might, however, been under-estimated. Recent findings reported, that nigral dopamine depletion in Parkinson's disease selectively weakens thalamic but not cortical afferents onto striatal projection neurons in the direct pathway (Tritsch and Carter, 2016). The cerebellum communicates via thalamus with the striatum and the pallidum (Hoshi et al., 2005; Hintzen et al., 2017). Under physiological conditions, these short latency connections to the BG are capable of facilitating optimal motor control by allowing to incorporate time-sensitive cerebellar information (Chen et al., 2014). In Parkinson's disease functional MRI studies indicated, that the cerebellum acts as compensatory system to the pathological BG output caused by nigral degeneration (Rascol et al., 1997; Liu et al., 2013). Parkinsonian patients have an impairment to produce self-initiated movements caused by a BG deficiency (Werheid et al., 2007; Wu and Hallett, 2005), especially in patients with akinetic-rigid Parkinson's disease (Rascol et al., 1997). In initial stages of the disease, PD patients are able to sustain externally triggered movements (Taniwaki et al., 2013); the deficiency of self-initiated movements can be compensated by externally triggered tasks, a typical cerebellar function. Interestingly, a recruitment of the cerebello-thalamo-cortical circuit increases concomitantly with Parkinson's disease progression (Sen et al., 2010). In more advanced stages compensatory functions break down, but can be maintained by external levodopa supply until no modulation of the cerebello-BG interaction is possible (Jech et al., 2013). This moved the view away from a cerebellar involvement in the solely generation of parkinsonian tremor, to other dysfunctions like e.g. akinesia or non-motor symptoms (Wu and Hallett, 2013). The here described dynamic in decline of this BG satellite system might therefore give additional information to the different clinical presentation of parkinsonian subtypes due to the altered D2 receptor signalling. Whereas wild type variants of the *ANNK1* gene demonstrated a lowered connectivity in both investigated pathways, the group with the at-risk allele showed, however, a different connectivity pattern with no significant decline in the nigro-striatal system, but with an increase of connectivity in the dentato-pallidal pathway following increasing motor impairment. These findings depict a potential compensatory role of the cerebellum differently to the nigro-striatal system in the A1 + group. Our results have, however, to be interpreted carefully due to the unfortunately limited sample size.

4.3. D2 polymorphism, motor impairment and medication response

Studies in healthy controls revealed, that the Taq1A polymorphism (rs1800497), representing the A1 allele of the *ANKK1* gene, evokes lowered striatal D2 availability in A1 + carriers relative to A1- homozygotes (Pohjalainen et al., 1998; Jönsson et al., 1999; Thompson et al., 1997). This polymorphism has been associated with disorders of self-regulation, such as obesity (Wang et al., 2001a; Comings, 1999), addiction (Berggren et al., 2006; Blum et al., 1990) and impaired executive function (Ariza et al., 2012).

In Parkinson's disease an allelic association between the Taq1A polymorphism and occurrence of the disease exists (Dai et al., 2014; Grevle et al., 2000; Oliveri et al., 2000), although it has been controversially discussed (Tan et al., 2003). In our study we quantified connectivity in PD patients in the A1- group and we found lower brain

connectivity (with hypothesized higher D2 receptor availability) in the nigro-striatal system than in the A1+ group, having no significant correlation with connectivity for motor impairment.

We also report differences in the medication response relating to the different gene variants. This finding is in line with actual studies showing that the D2 polymorphisms in Parkinson's disease have influence on the effect of dopaminergic medication. McDonell et al. (2018) reported, that patients with the rs1800497 Taq1A (A1) polymorphism (A1+) have improved proficiency to suppress impulsive actions when on dopamine agonists; conversely, patients with the A1− variant became less proficient at suppressing incorrect response information on dopamine agonists' therapy. However, Paus et al. (2008) demonstrated that the D2 Taq1A polymorphism alone has no pivotal role for inter-individual variability of dopaminergic requirement in Parkinson's disease. Influence of other D2 polymorphisms (rs1076560) onto the medication effect of L-DOPA has however been shown on motor and cognitive tasks (Kwak et al., 2013). And for rasagaline a favourable peak response in early Parkinson's disease has been described for other D2 receptor polymorphisms (rs2283265 and rs1076560), suggesting a different medication response for the individual gene variants (Masellis et al., 2016; Bhattacharjee et al., 2016). Next to the medication response also in the appearance of side effects the existence of the D2 receptor polymorphism seems to play a role, as shown for the increased risk of motor fluctuations (Wang et al., 2001b), dyskinesias (Oliveri et al., 1999) or hallucinations (Makoff et al., 2000). All these examples point towards a more personalized anti-parkinson therapy based on the underlying gene polymorphism.

5. Conclusion

To our knowledge, this is the first study combining results of basal ganglia connectivity measurement with D2 receptor signalling. Our findings point towards the possibility to predict the medication response of the individual patient by the combination of in vivo connectivity measures and the determination of the individual *ANKK1* gene variants; the incorporation of information of the individual genotype should be performed in larger cohorts integrating information about brain connectivity in the BG circuitry. This information might help to improve the individual therapeutic strategies for each patient and underscore the necessity of developing therapeutics aimed at axons as well as cell bodies so as to preserve their circuitry and function. Herewith, the prodromal detection of Parkinson's disease could enable the application of neuroprotective agents to hinder nigral cell death and the manifestation of parkinsonian symptoms (Postuma and Berg, 2016).

Data availability statement

Raw data were generated at Max-Planck-Institute for Metabolism Research Cologne, Germany, Gleueler Str. 50, 50,931 Cologne, Germany Derived data supporting the findings of this study are available from the corresponding author on request.

Financial disclosures

L. Timmermann is consultant for Medtronic Inc., Boston Scientific, Bayer Healthcare, UCB Schwarz Pharma, received honoraria in symposia sponsored by TEVA Pharma, Lundbeck Pharma, Bracco, Gianni PR, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, Boehringer Ingelheim, GlaxoSmithKline, Eumecom, Orion Pharma, Medtronic, Boston Scientific, Cephalon, Abott, GE Medical. The institution of Prof. Timmermann, not Prof. Timmermann himself, received funding by the German Research Foundation (DFG) via the Clinical Research Group 219, the German Ministry of Education and Research (BMBF), Manfred und Ursula Müller Stiftung, Klüh Stiftung, Hoffnungsbaum e. V., NBIA DISORDERS SOCIETY USA, the medical faculty of the University of Cologne via the “Köln Fortune program”, Medtronic Inc. and the German Parkinson Foundation (Deutsche Parkinson Vereinigung).

C. Eggers has received speaker's or consulting honoraria from Bial Inc., Daiichi Sankyo, GE Healthcare, Medtronic Inc., TEVA Pharma, UCB Pharma, Zambon Pharma.

In memoriam of Andreas Hintzen: sadly, Andreas deceased before we could finish this work—we would have greatly appreciated to accomplish this article together with him, and feel this as a tremendous loss. E.A.P, C.E., L.T., and M.T. were supported by funding of the German Research Foundation in the Clinical Research Group 219. M.T. is also supported by funding of the German Research Foundation in the transregional Collaborative Research Centre 134.

All funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Competing Interest

The authors have declared that no conflicts of interest exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101906.

References

Abeliovich, A., Gitler, A.D., 2016. Defects in trafficking bridge Parkinson's disease pathology and genetics. Nature 539 (7628), 207–216. https://doi.org/10.1038/nature20414. (PubMed PMID: 27830778).

Ariza, M., Garolera, M., Jurado, M.A., Garcia-Garcia, I., Hernan, I., Sánchez-Garre, C., et al., 2012. Dopamine genes (DRD2/ANKK1-TaqA1 and DRD4-7R) and executive function: their interaction with obesity. PLoS One 7 (7), e41482. https://doi.org/10.1371/journal.pone.0041482. PubMed PMID: 22848508; PubMed Central PMCID: PMCPMC3405092.

Atasoy, H., Nuyan, O., Tunc, T., Yorubulut, M., Unal, A.E., Inan, L.E., 2004. T2-weighted MRI in Parkinson's disease; substantia nigra pars compacta hypointensity correlates with the clinical scores. Neurol. India 52 (3), 332. http://www.neurologyindia.com/text.asp?2004/52/3/332/12730 (PubMed PMID: 9582487212107741542related:ZrlnZlnV-4QJ).

Behrens, T.E.J., Berg, H.J., Jbabdi, S., Rushworth, M.F.S., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? NeuroImage VL - IS - SP - EP 34 (1), 144–155. https://doi.org/10.1016/j.neuroimage.2006.09.018. (PubMed PMID: 17070705).

Berggren, U., Fahlke, C., Aronsson, E., Karanti, A., Eriksson, M., Blennow, K., et al., 2006. The taqI DRD2 A1 allele is associated with alcohol-dependence although its effect size is small. Alcohol Alcoholism (Oxford, Oxfordshire) 41 (5), 479–485. https://doi.org/10.1093/alcalc/agl043. (PubMed PMID: 16751215).

Bhattacharjee, S., Hughes, E., Ng, K.L., 2016. Rasagiline sensitive dopamine D2 receptor gene variants: a step forward toward more personalized antiparkinsonian therapy. Mov. Disord. Clin. Pract. 4 (2), 181–182. https://doi.org/10.1002/mdc3.12427. (PubMed PMID: 10.1002/mdc3.12427).

Blum, K., Noble, E.P., Sheridan, P.J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., et al., 1990. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 263 (15), 2055–2060. https://doi.org/10.1001/jama.1990.03440150063027. (PubMed PMID: 1969501).

Bostan, A.C., Dum, R.P., Strick, P.L., 2010. The basal ganglia communicate with the cerebellum. Proc. Natl. Acad. Sci. U. S. A. 107 (18), 8452–8456. https://doi.org/10.1073/pnas.1000496107. (PubMed PMID: 20404184; PubMed Central PMCID: PMCPMC2889518).

Braak, H., Del Tredici, K., 2004. Poor and protracted myelination as a contributory factor to neurodegenerative disorders. Neurobiol. Aging 25 (1), 19–23. https://doi.org/10.1016/j.neurobiolaging.2003.04.001.

Burke, R.E., O'Malley, K., 2012. Axon degeneration in Parkinson's disease. Exp. Neurol. https://doi.org/10.1016/j.expneurol.2012.01.011. (PubMed PMID: 22285449; PubMed Central PMCID: PMCPMC3340476).

Calabresi, P., Picconi, B., Tozzi, A., Di Filippo, M., 2007. Dopamine-mediated regulation of corticostriatal synaptic plasticity. Trends Neurosci. 30 (5), 211–219. https://doi.org/10.1016/j.tins.2007.03.001. (PubMed PMID: 17367873).

Carpenter, M.B., Peter, P., 1972. Nigrostriatal and nigrothalamic fibers in the rhesus monkey. J. Comp. Neurol. 144 (1), 93–115. https://doi.org/10.1002/cne.901440105. (PubMed PMID: 4623850).

Cazorla, M., de Carvalho, F.D., Chohan, M.O., Shegda, M., Chuhma, N., Rayport, S., et al., 2014. Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. Neuron 81 (1), 153–164. https://doi.org/10.1016/j.neuron.2013.10.041. (PubMed PMID: 24411738; PubMed Central PMCID: PMCPMC3899717).

Chen, C.H., Fremont, R., Arteaga-Bracho, E.E., Khodakhah, K., 2014. Short latency cerebellar modulation of the basal ganglia. Nat. Neurosci. 17 (12), 1767–1775. https://doi.org/10.1038/nn.3868. (PubMed PMID: 25402853; PubMed Central PMCID:

PMCPMC4241171).
Comings, D.E., 1999. Molecular heterosis as the explanation for the controversy about the effect of the DRD2 gene on dopamine D2 receptor density. Mol. Psychiatry 4 (3), 213–215. https://doi.org/10.1038/sj.mp.4000500. (PubMed PMID: 10.1038/sj.mp.4000500).
Cox, S.M.L., Frank, M.J., Larcher, K., Fellows, L.K., Clark, C.A., Leyton, M., et al., 2015. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. Neuroimage 109, 95–101. https://doi.org/10.1016/j.neuroimage.2014.12.070. (PubMed PMID: 25562824).
Dai, D., Wang, Y., Wang, L., Li, J., Ma, Q., Tao, J., et al., 2014. Polymorphisms of DRD2 and DRD3 genes and Parkinson's disease: a meta-analysis. Biomed. Rep. 2 (2), 275–281. https://doi.org/10.3892/br.2014.220. (PubMed PMID: 24649110; PubMed Central PMCID: PMCPMC3917740).
Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39 (6), 889–909. https://doi.org/10.1016/S0896-6273(03)00568-3.
Deffains, M., Iskhakova, L., Katabi, S., Haber, S.N., Israel, Z., Bergman, H., 2016. Subthalamic, not striatal, activity correlates with basal ganglia downstream activity in normal and parkinsonian monkeys. eLife 5https://doi.org/10.7554/eLife.16443. (PubMed PMID: 27552049; PubMed Central PMCID: PMCPMC5030093).
DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13 (7), 281–285. https://doi.org/10.1016/0166-2236(90)90110-V. (PubMed PMID: 1695404).
Eisenstein, S.A., Bogdan, R., Love-Gregory, L., Corral-Frías, N.S., Koller, J.M., Black, K.J., et al., 2016. Prediction of striatal D2 receptor binding by DRD2/ANKK1 TaqIA allele status. Synapse (New York, NY) 70 (10), 418–431. https://doi.org/10.1002/syn.21916. (PubMed PMID: 27241797; PubMed Central PMCID: PMCPMC4980198).
Fearnley, J.M., Lees, A.J., 1991. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5), 2283–2301. https://doi.org/10.1093/brain/114.5.2283. (PubMed PMID: 1933245).
Forstmann, B.U., Keuken, M.C., Jahfari, S., Bazin, P.-L., Neumann, J., Schäfer, A., et al., 2012. Cortico-subthalamic white matter tract strength predicts interindividual efficacy in stopping a motor response. Neuroimage 60 (1), 370–375. https://doi.org/10.1016/j.neuroimage.2011.12.044. (PubMed PMID: 160638496375223728related:rBj7EJ0GSxYJ).
Frank, M.J., Hutchison, K., 2009. Genetic contributions to avoidance-based decisions: striatal D2 receptor polymorphisms. Neurosci 164 (1), 131–140. https://doi.org/10.1016/j.neuroscience.2009.04.048. (PubMed PMID: 19393722; PubMed Central PMCID: PMCPMC2760598).
Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma, F.J.J., et al., 1990. D_1 and D_2 dopamine receptor-regulated gene expression of Striatonigral and Striatopallidal neurons. Science (New York, N.Y.) 250 (4), 1429–1432. https://doi.org/10.1126/science.2147780. (PubMed PMID: 10.1126/science.2147780).
Giompres, P., Delis, F., 2005. Dopamine transporters in the cerebellum of mutant mice. Cerebellum 4 (2), 105–111. https://doi.org/10.1080/14734220510007851. (PubMed PMID: 16035192).
Gluskin, B.S., Mickey, B.J., 2016. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. Transl. Psychiatry 6, e747. https://doi.org/10.1038/tp.2016.22. (PubMed PMID: 26926883; PubMed Central PMCID: PMCPMC4872447).
Gong, G., He, Y., Evans, A.C., 2011. Brain connectivity: gender makes a difference. Neurosci. 17 (5), 575–591. https://doi.org/10.1177/1073858410386492. (PubMed PMID: 21527724).
Grevle, L., Güzey, C., Hadidi, H., Brennersted, R., Idle, J.R., Aasly, J., 2000. Allelic association between the DRD2 TaqI a polymorphism and Parkinson's disease. Mov. Disord. 15 (6), 1070–1074. https://doi.org/10.1002/1531-8257(200011)15:6<1070::AID-MDS1003>3.0.CO;2-A. (PubMed PMID: 11104188).
Grillner, S., Robertson, B., 2016. The basal ganglia over 500 million years. Curr. Biol. 26 (20). https://doi.org/10.1016/j.cub.2016.06.041. R1088-R100. (PubMed PMID: 27780050).
Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. 20 (6), 2369–2382. https://doi.org/10.1523/JNEUROSCI.20-06-02369.2000. (PubMed PMID: 10704511).
Hintzen, A., Pelzer, E.A., Tittgemeyer, M., 2017. Thalamic interactions of cerebellum and basal ganglia. Brain Struct. Funct. 223 (2), 569–587. Epub 2. https://doi.org/10.1007/s00429-017-1584-y (PubMed PMID: 10.1007/s00429-017-1584-y).
Hoshi, E., Tremblay, L., Féger, J., Carras, P.L., Strick, P.L., 2005. The cerebellum communicates with the basal ganglia. Nat. Neurosci. 8 (11), 1491–1493. https://doi.org/10.1038/nn1544. (PubMed PMID: 16205719).
Howe, M.W., Dombeck, D.A., 2016. Rapid signalling in distinct dopaminergic axons during locomotion and reward. Nature 535 (7613), 505–510. https://doi.org/10.1038/nature18942. (PubMed PMID: 27398617; PubMed Central PMCID: PMCPMC4970879).
Ichinohe, N., Mori, F., Shoumura, K., 2000. A di-synaptic projection from the lateral cerebellar nucleus to the laterodorsal part of the striatum via the central lateral nucleus of the thalamus in the rat. Brain Res. 880 (1–2), 191–197. https://doi.org/10.1016/S0006-8993(00)02744-X. (PubMed PMID: 11033006).
Jbabdi, S., Sotiropoulos, S.N., Haber, S.N., Van Essen, D.C., Behrens, T.E., 2015. Measuring macroscopic brain connections in vivo. Nat. Neurosci. 18 (11), 1546–1555. https://doi.org/10.1038/nn.4134. (PubMed PMID: 10.1038/nn.4134).
Jech, R., Mueller, K., Schroeter, M.L., Růžička, E., 2013. Reply: levodopa increases functional connectivity in the cerebellum and brainstem in Parkinson's disease. Brain 136 (Pt 7). https://doi.org/10.1093/brain/awt015. e235-e. (PubMed PMID: 23370091).
Jönsson, E.G., Nöthen, M.M., Grünhage, F., Farde, L., Nakashima, Y., Propping, P., et al., 1999. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Mol. Psychiatry 4 (3), 290–296. https://doi.org/10.1038/sj.mp.4000532. (PubMed PMID: 10.1038/sj.mp.4000532).
Kakita, A., Takahashi, H., Homma, Y., Ikuta, F., 1994. Lewy bodies in the cerebellar dentate nucleus of a patient with Parkinson's disease. Pathol. Int. 44 (12), 878–880. https://doi.org/10.1111/j.1440-1827.1994.tb01688.x. (PubMed PMID: 7866573).
Kordower, J.H., Olanow, C.W., Dodiya, H.B., Chu, Y., Beach, T.G., Adler, C.H., et al., 2013. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. Brain 136 (Pt 8), 2419–2431. https://doi.org/10.1093/brain/awt192. (PubMed PMID: 23884810; PubMed Central PMCID: PMCPMC3722357).
Kravitz, A.V., Freeze, B.S., Parker, P.R.L., Kay, K., Thwin, M.T., Deisseroth, K., et al., 2010. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 466 (7), 622–626. https://doi.org/10.1038/nature09159. (PubMed PMID: 20613723; PubMed Central PMCID: PMCPMC3552484).
Kreitzer, A.C., Malenka, R.C., 2007. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. Nature 445 (7128), 643–647. https://doi.org/10.1038/nature05506. (PubMed PMID: 17287809).
Kwak, Y., Bohnen, N.I., Müller, M.L.T.M., Dayalu, P., Burke, D.T., Seidler, R.D., 2013. Task-dependent interactions between dopamine D2 receptor polymorphisms and L-DOPA in patients with Parkinson's disease. Behav. Brain Res. 245, 128–136. https://doi.org/10.1016/j.bbr.2013.02.016. (PubMed PMID: 23439215).
Lanciego, J.L., Luquin, N., Obeso, J.A., 2012. Functional neuroanatomy of the basal ganglia. Cold Spring Harbor Perspect. Med. 2 (12). https://doi.org/10.1101/cshperspect.a009621. a009621-a. (PubMed PMID: 10.1101/cshperspect.a009621).
Liu, H., Edmiston, E.K., Fan, G., Xu, K., Zhao, B., Shang, X., et al., 2013. Altered resting-state functional connectivity of the dentate nucleus in Parkinson's disease. Psychiatry Res. 211 (1), 64–71. https://doi.org/10.1016/j.pscychresns.2012.10.007. (PubMed PMID: 23352277).
Mai, J.K., Paxinos, G., Voss, T., 1997. Atlas of the Human Brain. Academic Press, San Diego.
Makoff, A.J., Graham, J.M., Arranz, M.J., Forsyth, J., LI, T., Aitchison, K.J., et al., 2000. Association study of dopamine receptor gene polymorphisms with drug-induced hallucinations in patients with idiopathic Parkinson's disease. Pharmacogenetics 10 (1), 43–48. https://insights.ovid.com/crossref?an=00008571-200002000-00006 (PubMed PMID: 10739171).
Masellis, M., Collinson, S., Freeman, N., Tampakeras, M., Levy, J., Tchelet, A., et al., 2016. Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson's disease: a pharmacogenetic study. Brain 139 (Pt 7), 2050–2062. https://doi.org/10.1093/brain/aww109. (PubMed PMID: 27190009).
Matsuda, W., Furuta, T., Nakamura, K.C., Hioki, H., Fujiyama, F., Arai, R., et al., 2009. Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. J. Neurosci. 29 (2), 444–453. https://doi.org/10.1523/JNEUROSCI.4029-08.2009. (PubMed PMID: 19144844).
McDonell, K.E., van Wouwe, N.C., Harrison, M.B., Wylie, S.A., Claassen, D.O., 2018. Taq1A polymorphism and medication effects on inhibitory action control in Parkinson disease. Brain Behav. 8 (7), e01008. https://doi.org/10.1002/brb3.1008. (PubMed PMID: 29856137; PubMed Central PMCID: PMCPMC6043698).
McGuire, V., Van Den Eeden, S.K., Tanner, C.M., Kamel, F., Umbach, D.M., Marder, K., et al., 2011. Association of DRD2 and DRD3 polymorphisms with Parkinson's disease in a multiethnic consortium. J. Neurol. Sci. 307 (1–2), 22–29. https://doi.org/10.1016/j.jns.2011.05.031. (PubMed PMID: 21663922; PubMed Central PMCID: PMCPMC3155471).
Menke, R.A., Jbabdi, S., Miller, K.L., Matthews, P.M., Zarei, M., 2010. Connectivity-based segmentation of the substantia nigra in human and its implications in Parkinson's disease. Neuroimage 52 (4), 1175–1180. https://doi.org/10.1016/j.neuroimage.2010.05.086. (PubMed PMID: 20677376).
Morel, A., 2007. Stereotactic Atlas of the Human Thalamus and Basal Ganglia. Informa HealthCare USA, Inc, NewYork (Apr 30. 149 p).
Naidich, T.P., Duvernoy, H.M., Delman, B.N., Sorensen, A.G., Kollias, S.S., Haacke, E.M., 2009. Duvernoy's Atlas of the Human Brain Stem and Cerebellum. Springer Verlag (876 p).
Neville, M.J., Johnstone, E.C., Walton, R.T., 2004. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum. Mutat. 23 (6), 540–545. https://doi.org/10.1002/humu.20039. (PubMed PMID: 15146457).
Noble, E.P., Gottschalk, L.A., Fallon, J.H., Ritchie, T.L., Wu, J.C., 1997. D2 dopamine receptor polymorphism and brain regional glucose metabolism. Am. J. Med. Genet. 74 (2), 162–166. https://doi.org/10.1002/(SICI)1096-8628(19970418)74:2<162::AID-AJMG9>3.3.CO;2-3. (PubMed PMID: 9129716).
Obeso, J.A., Marin, C., Rodriguez-Oroz, C., Blesa, J., Benitez Temino, B., Mena-Segovia, J., et al., 2008. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann. Neurol. 64 (Suppl 2(S2)), S30–S46. https://doi.org/10.1002/ana.21481. (PubMed PMID: 19127584).
Obeso, J.A., Rodriguez-Oroz, M.C., Goetz, C.G., Marin, C., Kordower, J.H., Rodriguez, M., et al., 2010. Missing pieces in the Parkinson's disease puzzle. Nat. Med. 16 (6), 653–661. https://doi.org/10.1038/nm.2165. (PubMed PMID: 20495568).
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.
Oliveri, R.L., Annesi, G., Zappia, M., Civitelli, D., Montesanti, R., Branca, D., et al., 1999. Dopamine D2 receptor gene polymorphism and the risk of levodopa-induced dyskinesias in PD. Neurology 53 (7), 1425–1430. https://doi.org/10.1212/WNL.53.7.1425. (PubMed PMID: 10534246).
Oliveri, R.L., Annesi, G., Zappia, M., Civitelli, D., De Marco, E.V., Pasqua, A.A., et al., 2000. The dopamine D2 receptor gene is a susceptibility locus for Parkinson's disease. Mov. Disord. 15 (1), 120–126. https://doi.org/10.1002/1531-8257(200001)

15:1 < 120::aid-mds1019 > 3.0.co;2-s. (PubMed PMID: 10.1002/1531-8257(200001) 15:1 < 120::aid-mds1019 > 3.0.co;2-s).
O'Malley, K.L., 2010. The role of axonopathy in Parkinson's disease. Exp. Neurobiol. 19 (3), 115–119. https://doi.org/10.5607/en.2010.19.3.115. (PubMed PMID: 22110350; PubMed Central PMCID: PMCPMC3214783).
Parish, C.L., Finkelstein, D.I., Drago, J., Borrelli, E., Horne, M.K., 2001. The role of dopamine receptors in regulating the size of axonal arbors. J. Neurosci. 21 (14), 5147–5157. https://doi.org/10.1523/JNEUROSCI.21-14-05147.2001. (PubMed PMID: 11438590).
Parker, J.G., Marshall, J.D., Ahanonu, B., Wu, Y.-W., Kim, T.H., Grewe, B.F., et al., 2018. Diametric neural ensemble dynamics in parkinsonian and dyskinetic states. Nature 557 (7704), 177–182. https://doi.org/10.1038/s41586-018-0090-6. (PubMed PMID: 10.1038/s41586-018-0090-6).
Paulus, W., Jellinger, K., 1991. The neuropathologic basis of different clinical subgroups of Parkinson's disease. J. Neuropathol. Exp. Neurol. 50 (6), 743–755. https://doi.org/10.1097/00005072-199111000-00006. (PubMed PMID: 32760257541124181 48related:ZOHm9BDIdi0J).
Paus, S., Grünewald, A., Klein, C., Knapp, M., Zimprich, A., Janetzky, B., et al., 2008. The DRD2 TaqIA polymorphism and demand of dopaminergic medication in Parkinson's disease. Mov. Disord. 23 (4), 599–602. https://doi.org/10.1002/mds.21901. (PubMed PMID: 18175338).
Pelzer EA, Hintzen A, Goldau M, von Cramon DY, Timmermann L, Tittgemeyer M. Cerebellar networks with basal ganglia: feasibility for tracking cerebello-pallidal and subthalamo-cerebellar projections in the human brain. Eur. J. Neurosci.. 2013;38(8):3106–14. doi: https://doi.org/10.1111/ejn.12314. (PubMed PMID: 23879686).
Pelzer, E.A., Melzer, C., Timmermann, L., von Cramon, D.Y., Tittgemeyer, M., 2017. Basal ganglia and cerebellar interconnectivity within the human thalamus. Brain Struct. Funct. 222 (1), 381–392. https://doi.org/10.1007/s00429-016-1223-z. (PubMed PMID: 27089884; PubMed Central PMCID: PMCPMC5225161).
Pohjalainen, T., Rinne, J.O., Någren, K., Lehikoinen, P., Anttila, K., Syvälahti, E.K., et al., 1998. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry 3 (3), 256–260. https://doi.org/10.1038/sj.mp.4000350. (PubMed PMID: 9672901).
Postuma, R.B., Berg, D., 2016. Advances in markers of prodromal Parkinson disease. Nat. Rev. Neurol. 12 (11), 622–634. https://doi.org/10.1038/nrneurol.2016.152. (PubMed PMID: 27786242).
Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., et al., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30 (12), 1591–1601. https://doi.org/10.1002/mds.26424. (PubMed PMID: 10.1002/mds.26424).
Rascol, O., Sabatini, U., Fabre, N., Brefel, C., Loubinoux, I., Celsis, P., et al., 1997. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. Brain 120 (Pt 1), 103–110. https://doi.org/10.1093/brain/120.1.103. (PubMed PMID: 9055801).
Reese, T.G., Heid, O., Weisskoff, R.M., Wedeen, V.J., 2003. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. Magn. Reson. Med. 49 (1), 177–182. https://doi.org/10.1002/mrm.10308. (PubMed PMID: 12509835).
Reynolds, J.N., Hyland, B.I., Wickens, J.R., 2001. A cellular mechanism of reward-related learning. Nature 413 (6851), 67–70. https://doi.org/10.1038/35092560. (PubMed PMID: 11544526).
Schaltenbrand, G., Wahren, W., 1977. Atlas for Stereotaxy of the human brain. Stuttgart 84 updated Nov 28; cited 2.
Schmahmann, J.D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A.S., et al., 1999. Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. Neuroimage 10 (3 Pt 1), 233–260. https://doi.org/10.1006/nimg.1999.0459.
Sen, S., Kawaguchi, A., Truong, Y., Lewis, M.M., Huang, X., 2010. Dynamic changes in cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease. Neurosci 166 (2), 712–719. https://doi.org/10.1016/j.neuroscience.2009.12.036. (PubMed PMID: 20034546; PubMed Central PMCID: PMCPMC2852615).
Shen, W., Flajolet, M., Greengard, P., Surmeier, D.J., 2008. Dichotomous dopaminergic control of striatal synaptic plasticity. Science (New York, N.Y.) 321 (5890), 848–851. https://doi.org/10.1126/science.1160575. (PubMed PMID: 18687967; PubMed Central PMCID: PMCPMC2833421).
Smith, C.T., Dang, L.C., Buckholtz, J.W., Tetreault, A.M., Cowan, R.L., Kessler, R.M., et al., 2017. The impact of common dopamine D2 receptor gene polymorphisms on D2/3 receptor availability: C957T as a key determinant in putamen and ventral striatum. Transl. Psychiatry 7 (4), e1091. https://doi.org/10.1038/tp.2017.45. (PubMed PMID: 28398340; PubMed Central PMCID: PMCPMC5416688).
Tagliaferro, P., Burke, R.E., 2016. Retrograde axonal degeneration in Parkinson disease. J. Park. Dis. 6 (1), 1–15. https://doi.org/10.3233/JPD-150769. (PubMed PMID: 27003783; PubMed Central PMCID: PMCPMC4927911).
Tan, E.-K., Tan, Y., Chai, A., Tan, C., Shen, H., Lum, S.-Y., et al., 2003. Dopamine D2 receptor TaqIA and TaqIB polymorphisms in Parkinson's disease. Mov. Disord. 18 (5), 593–595. https://doi.org/10.1002/mds.10406. (PubMed PMID: 10.1002/mds.10406).
Taniwaki, T., Yoshiura, T., Ogata, K., Togao, O., Yamashita, K., Kida, H., et al., 2013. Disrupted connectivity of motor loops in Parkinson's disease during self-initiated but not externally-triggered movements. Brain Res. 1512, 45–59. https://doi.org/10.1016/j.brainres.2013.03.027. (PubMed PMID: 23548595).
Theisen, F., Leda, R., Pozorski, V., Oh, J.M., Adluru, N., Wong, R., et al., 2017. Evaluation of striatonigral connectivity using probabilistic tractography in Parkinson's disease. NeuroImage Clin. 16, 557–563. https://doi.org/10.1016/j.nicl.2017.09.009. (PubMed PMID: 28971007; PubMed Central PMCID: PMCPMC5608174).
Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E.K., et al., 1997. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 7 (6), 479–484. https://doi.org/10.1097/00008571-199712000-00006. (PubMed PMID: 9429233).
Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25 (15), 2649–2653. https://doi.org/10.1002/mds.23429. (PubMed PMID: 21069833).
Trimmer, P.A., Schwartz, K.M., Borland, M.K., De Taboada, L., Streeter, J., Oron, U., 2009. Reduced axonal transport in Parkinson's disease cybrid neurites is restored by light therapy. Mol. Neurodegener. 4 (1), 26. https://doi.org/10.1186/1750-1326-4-26. (PubMed PMID: 19534794; PubMed Central PMCID: PMCPMC2711937).
Tritsch, N.X., Carter, A.G., 2016. Parkinson's disease: a Thalamostriatal rebalancing act? Neuron 89 (4), 675–677. https://doi.org/10.1016/j.neuron.2016.02.008. (PubMed PMID: 26889806).
Wang, G.J., Volkow, N.D., Logan, J., Pappas, N.R., Wong, C.T., Zhu, W., et al., 2001a. Brain dopamine and obesity. Lancet 357 (9253), 354–357. https://doi.org/10.1016/S0140-6736(00)03643-6. (PubMed PMID: 11210998).
Wang, J., Liu, Z.L., Chen, B., 2001b. Association study of dopamine D2, D3 receptor gene polymorphisms with motor fluctuations in PD. Neurology 56 (12), 1757–1759. https://doi.org/10.1212/wnl.56.12.1757. (PubMed PMID: 11425949).
Werheid, K., Koch, I., Reichert, K., Brass, M., 2007. Impaired self-initiated task preparation during task switching in Parkinson's disease. Neuropsychologia 45 (2), 273–281. https://doi.org/10.1016/j.neuropsychologia.2006.07.007. (PubMed PMID: 16945394).
Wu, T., Hallett, M., 2005. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 128 (10), 2250–2259. https://doi.org/10.1093/brain/awh569. (PubMed PMID: 17011118919993940626related:kloqaoeiE-wJ).
Wu, T., Hallett, M., 2013. The cerebellum in Parkinson's disease. Brain 136 (Pt 3), 696–709. https://doi.org/10.1093/brain/aws360. (PubMed PMID: 23404337).
Zhang, Y., Bertolino, A., Fazio, L., Blasi, G., Rampino, A., Romano, R., et al., 2007. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc. Natl. Acad. Sci. U. S. A. 104 (51), 20552–20557. https://doi.org/10.1073/pnas.0707106104. (PubMed PMID: 18077373; PubMed Central PMCID: PMCPMC2154469).